(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 300 282**
A1

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: 88110561.7

(22) Date of filing: 07.07.88

(51) Int. Cl.4: **A61K 7/48 , A61K 7/40 , A61K 9/06 , A61K 31/35**

Claims for the following Contracting State: GR.

(30) Priority: 10.07.87 IT 2125387

(43) Date of publication of application: 25.01.89 Bulletin 89/04

(84) Designated Contracting States: AT BE CH DE FR GB GR IT LI LU NL SE.

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(54) **Pharmaceutical and cosmetic compositions containing complexes of flavanolignans with phospholipids.**

(57) Topical pharmaceutical or cosmetic compositions having eutrophic and cutis-protecting activities, based on complexes of silybin, silydianin, silychristin or mixtures thereof with vegetal or synthetic phospholipids.

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PHARMACEUTICAL AND COSMETIC COMPOSITIONS CONTAINING COMPLEXES OF FLAVANOLIGNANS WITH PHOSPHOLIPIDS

The present invention relates to topical pharmaceutical or cosmetic compositions, containing complexes of flavanoligans with phospholipids.

Flavanoligans extracted from a thistle, Silybum marianum, namely silybin, silydianin and silychristin as well as the admixture thereof in precise ratios, which admixture is known as silymarin, and also certain extracts, are used in human therapy because of the hepato-protecting and detoxicant activity thereof, which is at least partly connected to a stabilizing and protecting action for the hepatocyte membrane.

E.P.A. 0209038 discloses phospholipidic complexes of said flavanolignant which, in comparison with the free, uncomplexed form, show advantages as regard bioavailability after oral administration.

Now, it has been surprisingly found that the same complexes, or those obtainable from Silybum marianum extracts, may be advantageously used in topical pharmaceutical or cosmetic compositions, useful to counteract degenerative and aging phenomena of cutis: said activity, which of course cannot be related to the one traditionally known in hepatology, may find useful applications in the dermatologic field, for example to promote healing process, in the treatment of erythemae, burns, dystrophic conditions of cutis or mucosae, dermatitis, etc. or in the cosmetic field to counteract cutis aging and to protect cutis from atmospheric and environmental agents (rays, wind, sun, etc.).

The activities disclosed in the present invention, particularly the inhibiting activity of aging injuries, seem to be at least partly related to the ability of phospholipidic complexes of flavanoligans to act as free radical scavengers.

In fact, it is already known the remarkable role played by free radicals, which derive from certain cellular metabolisms or from damaging agents such as radiations, etc. in processes related to aging, due to injuring effects on cellular structures of various tissues.

Anyway, the validity of the invention is not connected to the verification of the above assumed mechanism of action.

In the compositions according to the invention, complexes of silymarin or of one or more of its components with natural soy lecithins, such as those defined under the commercial names Lipoid S 30 or Epicuron 100, consisting of mixtures of phosphatidylcholine, phosphatidylserine and phosphatidylethanolamine, wherein the acyl residues derive mainly from palmitic, stearic, oleic and linoleic acids are preferably used.

The use of natural phospholipids (from soy or animal tissues) is particularly preferred for cosmetic applications, while for more specifically pharmaceutical formulations the use of a chemically homogeneous and defined phospholipid, e.g. distearoyl phosphatidylcholine, may be more appropriate.

The preparation of complexes, which is described in EP 0209038, is carried out by reacting 0,3-2 mole, prefe rably about 1 mole, of the phospholipid with 1 mole of silybin, silydianin or silychristin, alone or in natural admixture (silymarin), in aprotic organic solvents, such as dioxane, acetone, etc. from which solvents the complex may be recovered by precipitation with non-solvents, such as aliphatic hydrocarbons, or by lyophilization or by nebulization.

Preparation of the formulations according to the invention is carried out by means of conventional techniques and excipients, as described in "Remington's Pharmaceutical Sciences Handbook", Hack Pub. Co., N.Y. U.S.A.

Phospholipid complexes of flavanoligans may be used also in form of microdispersions in water, which are obtained by homogenization by means of high-speed or ultra-sonic stirrers, said microdispersions being optionally added with thickening or suspending agents.

Examples of suited formulations comprise creams, gels, ointments, lotions or other formulations conventionally used for topical administration. It is also possible to envisage plasters, gauzes, pads or garments imbued with the above mentioned active principles.

Other known active ingredients, having complementary or anyway useful activities for the intended therapeutic and/or cosmetic uses, may be present besides the phospholipid complexes of flavanoligans.

For example, the compositions of the invention may optionally contain vitamins, amino acids, vegetal extracts, emollients, antibacterial agents, topical anti-inflammatory agents, etc.

Phospholipid complexes of silymarin or of the components thereof will be present in the formulations of the invention at percentages from 1 to 10 by weight. The administration procedures will obviously depend on the particular selected form and on the type of administration: generally, it will be sufficient to cover the cutis area to be treated with a thin layer of cream, gel or lotion 1 to 3 times a day, for times even longer than some months.

The following non-limiting examples further illustrate the invention.

PREPARATION 1

Silymarin-soy phosphatidylcholine 1:1 complex.

A solution of 5 g of silymarin in 100 ml of acetone was treated with 8 g of "Lipoid S 100 (R)", under stirring at room temperature. After complete solubilization, the raction mixture was concentrated under vacuum to 30 ml and poured into 300 ml of ligroin, under stirring. The precipitate was left to settle overnight, then it was collected by filtration, washed with ligroin and dried under vacuum at 40°C. 11.2 g of the complex were obtained. $E_{1\%}$ = 170.2 at 288 nm (CH_3OH).

PREPARATION 2

Silybin-soy phosphatidylcholine 1:2 complex.

A suspension of 4.82 g of silybin (0.010 mole) in 75 ml of dioxane was treated under stirring with a suspension containing 15.4 g (0.020 mole) of "Lipoid S 100 (R)". After 4 hours the reaction mixture became clear and it was lyophilized. 20 g of the complex of light yellow colour, was obtained.
$E_{1\%}$ = 106 at 288 nm (CH_3OH).
E1. Analysis (MW = 2022)
calc. % N = 1.38; P = 3.07
found % N = 1.35; P = 3.11

PREPARATION 3

Silybin-soy phosphatidylcholine 1:0.3 complex.

A solution of 2.41 g (0.005 mole) of silybin in 100 ml of dioxane was treated at 60°C with 0.770 g (0.001 mole) of "Lipoid S 100 (R)" for 1 hour. The reaction mixture was evaporated to dryness under vacuum and the residue was taken up into 100 ml of chloroform.

Uncomplexed silybin, present as sediment, was removed by filtration and mother liquors containing the complex were evaporated to dryness under vacuum.

The obtained residue, dried at 30°C under vacuum, consisted of 2.3 g of the complex, in form of a white yellowish powder.
$E_{1\%}$ = 300 at 288 nm (CH_3OH).

PREPARATION 4

A solution of 10 g of silymarin in 150 ml of acetone was treated with 20 g of "Lipoid S 100 (R)" under stirring at room temperature.

After complete dissolution, the reaction mixture was concentrated to small volume under vacuum.

The viscous residue was dried under vacuum at 45° C during a night. 29 g of the product was obtained, which was yellow-beige in colour and spectroscopically agreed with complex from EP 0209038.

PREPARATION 5

Silymarin-distearoylphosphatidylcholine 1:1 complex

A solution of 10 g of silymarin in 150 ml of acetone was treated with 10 g of distearoylphosphatidylcholine under stirring at room temperature. The reaction mixture was evaporated to small volume under vacuum. The viscous residue was washed with ligroin and dried under vacuum at 40° C; 18.8 g of a product, whose spectroscopical data were in agreement with a complex structure, were obtained.

The activities of the compositions according to the invention are illustrated as an example, by the comparison of the effect on croton oil oedema of silymarin, silymarin-distearoylphosphatidylcholine complex (according to preparation 5), distearoylphosphatidylcholine and indomethacine.

The data reported in the table which follows show that local application of silymarin and to a greater extent of the silymann-distearoylphosphatidylcholine complex cause a dose-dependent anti-oedema action, well comparable with the indomethacine's one.

On the contrary, distearoylphosphatidylcholine starts a modest activity, largely inferior to the one of the silymarin-distearoylphosphatidylcholine.

TEST FROM CROTON OIL (Tubaro et al., Agents Actions 17, 347, 1985)

Animals. Male mice of albino race, Swiss stock CD 1 Charles River.

Method. Application of croton oil and of the substance under exam. in ethyl acetate solution, on the internal surface of the mouse's right ear.

At the end of the experiment, that is 6 h after application of croton oil and of the substance under exam. the animals were sacrificed. Evaluation of the oedema answer was carried out by measuring the difference in weight between a well defined area taken from the treated ear and an analogous one taken from the untreated ear.

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SUBSTANCES	No. ANIMALS	DOSE/EAR mcg	OEDEMA ± ES mg	% REDUCTION	P< (ANOV-A)
Controls	27	67.5	7.1 ± 0.2	-	-
Silymarin	14	480	2.2 ± 0.4	69.0	0.001
	13	240	3.0 ± 0.4	59.5	0.001
	13	120	4.5 ± 0.5	39.2	0.001
	14	48	6.2 ± 0.3	12.7	0.005
Silymarin/distearoylphosphatidylcholine	14	1270	0.5 ± 0.2	93.0	0.001
	14	635	0.8 ± 0.2	89.2	0.001
	14	317	3.9 ± 0.5	47.3	0.001
	14	127	3.7 ± 0.6	47.9	0.001
Distearoylphosphatidylcholine	14	790	5.2 ± 0.5	26.8	0.001
	14	395	6.5 ± 0.3	8.5	0.05
	13	197	5.9 ± 0.3	16.9	0.001
	14	79.	6.3 ± 0.3	11.3	0.01
Indomethacine	13	142	4.7 ± 0.8	33.8	0.001

Some examples of formulations according to the invention are reported hereinbelow.

EXAMPLE 1

Cream containing a silymarin-soy phosphatidylcholine complex as the active ingredient.

Formulation for 100 g of cream

Complex of preparation 1 2.0 g
Polyethyleneglycol 2 g
Polysorbate 80 3 g
Cetyl alcohol 10 g
Wheat germ oil 2 g
Silicon oil 350 cps 0.5 g
Antioxidants (oxinex[A] 2004) 0.1 g
Carboxyvinylpolymer (Carbomer 934[B]) 0.8
Triethanolamine 1.2 g
Preservants (a mixture of methyl and propyl p-hydroxybenzoates) 0.2 g
Perfumed composition 0.1 g
Depurated water q.s. to 100 g

EXAMPLE 2

Gel containing a silybin-soy phosphatidylcholine complex as the active ingredient.

Formulation for 100 g of gel

Complex of preparation 2 1 g
Imidazolidinylurea 0.3 g
Octilinone 0.1 g
C_8-C_{12} ethoxylated triglycerids (Softigen 767®) 25 g
Polyoxyethylene 20 oleylether 5 g
Carboxyvinylpolymer (Carbomer 934®) 1.5 g
Triethanolamine 2 g
Perfumed composition 0.1 g
Depurated water 65 g

EXAMPLE 3

Lotion containing a silymarin-soy phosphatidylcholine complex as the active ingredient.

Formulation for 100 g of lotion

Complex of preparation 4 1 g
Imidazolidinylurea 0.3 g
Octilinone 0.1 g
PEG-8-caprylic-capric glyceride 25 g
Polyoxyethylene 20 oleylether 5 g
Perfumed composition 0.1 g
Water q.s. to 100 g

Claims

1. Topical pharmaceutical or cosmetic compositions containing as the active ingredient flavanolignans complexes, selected from the group consisting of silymarin, silybin, silydianin and silychristin, with natural or synthetic phospholipids, in admixture with appropriate excipients.

2. Compositions according to claim 1, wherein the flavanolignan is silymarin.

3. Compositions according to claim 1, wherein the flavanolignan is silybin.

4. Compositions according to anyone of claims 1-3, wherein the phospholipid is soy phosphatidylcholine.

5. Compositions according to anyone of the preceeding claims, in form of lotions, creams, gels or ointments.

6. Compositions according to anyone of the preceeding claims, wherein the active ingredient is present in form of a microdispersion in water.

7. Compositions according to anyone of the preceeding claims, wherein the active ingredient is present at concentrations varying from 1% to 10% by weight.

8. Use of phospholipid complexes of flavanolignans for the preparation of dermatologic or cosmetic medicaments for cutaneous administration.

Claims for the following Contracting State: GR

1. Topical cosmetic compositions containing as the active ingredient flavanolignans complexes, selected from the group consisting of silymarin, silybin, silydianin and silychristin, with natural or synthetic phospholipids, in admixture with appropriate excipients.

2. Compositions according to claim 1, wherein the flavanolignan is silymarin.

3. Compositions according to claim 1, wherein the flavanolignan is silybin.

4. Compositions according to anyone of claims 1-3, wherein the phospholipid is soy phosphatidylcholine.

5. Compositions according to anyone of the preceeding claims, in form of lotions, creams, gels or ointments.

6. Compositions according to anyone of the preceeding claims, wherein the active ingredient is present in form of a microdispersion in water.

7. Compositions according to anyone of the preceeding claims, wherein the active ingredient is present at concentrations varying from 1% to 10% by weight.

8. Use of phospholipid complexes of flavanolignans for the preparation of cosmetics for cutaneous administration.

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EUROPEAN SEARCH REPORT

Application Number

EP 88 11 0861

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,Y	EP-A-0 209 038 (INVERNI DELLA BEFFA SPA) * The whole document * ---	1-8	A 61 K 7/48 A 61 K 7/40 A 61 K 9/06
Y	EP-A-0 180 505 (CLARINS) * Abstract; page 4, lines 16-19; page 5, lines 1-3; page 8, line 26 - page 9, line 21 * ---	1-8	A 61 K 31/35
A	ARZNEIMITTELFORSCHUNG, vol. 18, no. 6, June 1968, pages 698-704, Editio Cantor K.G., Aulendorf/Württ., DE; G.HAHN et al.: "Zur Pharmakologie und Toxikologie von Silymarin des antihepatotoxischen Wirkprinzipes aus Silybum marianum (L.) Gaertn" * Page 698, chapter: "Zur Geschichte"; page 703, summary * ---	1-8	
A	FR-A-2 343 481 (N.GERLICH) * Claim 1 * -----	1-8	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K
C 07 D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	20-10-1988	MUELLNERS W.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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